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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/826,609 | 04/05/2001 | Bruce L. Roberts | GA0150C | 4367 |

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| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/826,609 | ROBERTS ET AL. | |
| | Examiner | Art Unit | |
| | Karen A Canella | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *8-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-5, 7 and 25 have been amended. Claims 8-24 remain withdrawn from consideration. Claims 1-7, 25 and 26 are under consideration.

2. Text of sections of Title 35, US Code not found in this action can be found in a prior Office action.

3. Acknowledgement is made of applicants amendment of the priority of the instant application to a continuation of PCT/US99/23166, filed October 4, 1999, rather than using PCT/US99/23166 as a application under 119(a-d or f).

4. Applicant argues that the instant specification is entitled to the effective filing date of the provisional application 60/103,220 as the disclosure of the cdc2-related protein kinase or integrin alpha-3 are relevant to the instant invention. Applicant further argues that it is inappropriate that the examiner questions the priority claim of the instant application because intervening art was not in question. This has been considered but not found persuasive. The section of the M.P.E.P quoted by the applicant is in reference to a claim for foreign priority not US priority. Section 2163 of the M.P.E.P. states:

> A question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently (see, e.g., > Enzo Biochem, 296 F.3d at 1329, 63 USPQ2d at 1616 (Fed. Cir. 2002);< Eli Lilly, 119 F.3d 1559, 43 USPQ2d 1398), a new or amended claim wherein a claim limitation has been added or removed, or a claim to entitlement of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c).

Thus applications claiming and earlier effective filing date via 119(e) must conform to the written description requirement of 112, first paragraph. As stated in the previous Office action, the '220 application fails to adequately describe the claimed genus of all tumor antigens as only cdc2 or integrin-alpha is discussed and no mention is made of a wider genus of tumor antigens within the context of the claimed method.

Accordingly the instant application will be given the effective priority date of PCT/US99/23166 (

5. The objection to the oath/declaration is maintained until such time as the new oath/declaration is submitted.

6. Claim 4 section d and claim 5 section e recites "administering if said" rather than "administering said".

7. The rejection of claims 2-7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.
(A)It is unclear how claims 2-6 further limit claim 1 as there is no nexus between the administration of the protein, gene delivery vehicle, immune effector cells or antibodies to a subject as recited in claims 2-7 and the method objective of claim 1 which is the identification of a putative cancer therapeutic.
(B)The metes and bounds of claim 1, 4 and 5 cannot be determined as it is unclear what the "putative cancer therapeutic" is at the conclusion of the claim: it is unclear if the polynucleotide, the protein or fragment thereof of claim 1 would be the putative cancer therapeutic, it is unclear if the "immune effector cells" of claim 4 are the putative cancer therapeutic; it is unclear if the antibody of claim 5 is the putative cancer therapeutic.
(C) Claims 4 and 5 are vague and indefinite in the recitation of "determining if said immure effector cells are immunogenic" and "determining if said antibodies are immunogenic". The definition of "immunogenic" is "The potential of an antigen (or immunogen) to stimulate an immune response in a given species of animal. Immunogenicity depends of the size of the antigen and the extent to which its antigenic determinants differ from the immunized animal" (Herbert et al, Ed.s, Dictionary of Immunology, 3rd Edition, 1985, page 116). Thus, if an antibody or effector cell of claims 4 and 5 were to be immunogenic, an immune response would be generated in the host against the antibody or effector cell.

(D)Claim 7 fails to provide an active method step for "designing a cancer vaccine corresponding to said amino acid sequence". Claim 7 states "the improvement comprising" in the method pre-amble but fails to state with what method the "improvement" is in reference to. Further the claim is vague and indefinite in the recitation of "identifying an amino acid sequence not known to be antigenic". The M.P.E.P states that the claims should set the metes and bounds of the claimed subject matter by indicating what the product is, not by indicating what the product is not. Thus the limitation of "not known to be antigenic" is what the product is not, rendering the claim vague and indefinite.

8. Claims 1, 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a putative cancer therapeutic that stimulates a cell mediated immune response, does not reasonably provide enablement for a method of identifying a putative cancer therapeutic that stimulates a humoral response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Claim 5 is dependent on claim 1 and recites the specific limitation of administering antibodies which elicit an immune response against the target cancer cells. Claims 1 and 5 thus encompasses the generation of an anti-idiotypic immune response. The art teaches the necessity of developing a cell-mediated immune response in cancer immunotherapy (for example see the abstract of Becker et al, Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3287 and the abstract of Dudley et al (Journal of Immunotherapy, Jul 1999, Vol. 22, pp. 288-298). The art teaches that administration of tumor antigens or fragments thereof to patients having circulating antibodies which bind to said antigens or fragments hinders a cellular immune response because the antibodies present in the serum bind to the proteins or fragment, routing the antibody protein complex or the antibody fragment complex to the class II pathway resulting in a humoral cell response to the exclusion of the class I pathway which would result in a cellular immune response (Apostolopoulos et al, Nature Medicine, 1998, Vol. 4, pp. 315-320).

Thus, given the teachings of the prior art regarding the necessity of developing a cell-mediated CTL response and the undesirability of developing a humoral response to a cancer associated antigen, one of skill in the art would not be able to use the invention of claim 5 and the invention of claim 1 to the extent that it include the induction of an immune response to an antibody directed against a tumor associated antigen.

9. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 2 is dependent on claim 1 and requires the administration of a gene delivery vector to a subject. The specification is not enabling for said gene delivery vector for the following reasons:

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the

vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ( "Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be

subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

10. Claims 1, 3, 4, 7, 25 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Scanlan et al (US 6,686,147 B1, priority to July 15, 1998).

Claim 1 is drawn to a method to identify a putative cancer therapeutic comprising the steps in the order of identifying a polynucleotide which is uniquely expressed or over expressed in a target human cancer cell as compared with a control non-cancer cell; determining the protein corresponding to said identified polynucleotide; determining if said protein or fragment thereof is immunogenic; wherein the ability of said protein or fragment thereof to elicit and immune response against said target cancer cell is indicative of a cancer therapeutic effect by said protein or fragment thereof. Claim 3 embodies the method of claim 1 further comprising a step wherein said immunogenic protein or fragments thereof is administered to a subject in an antigen presenting cell. Claim 4 embodies the method of claim 1 further comprising the steps of generating immune effector cells reactive with an immunogenic protein and determining if said immure effector cells are immunogenic; wherein the ability of said immune effector cells to elicit an immune response against said target cancer cell ix indicative of a putative cancer therapeutic.

Claim 7 is drawn to a method to design a cancer vaccine from a sample obtaining for a subject suffering from cancer, the improvement comprising first identifying an amino acid sequence which is not known to be antigen, but which is uniquely expressed or over expressed in a human target cancer cell from said subject, as compared with a control non-cancer cell secondly determining if said amino acid sequence is capable of eliciting an immune response against said target cancer cell and designing a cancer vaccine corresponding to said amino acid sequence.

Claims 25 is drawn to a method to identify a putative cancer therapeutic comprising the steps of identifying a polynucleotide which is expressed at a higher level in a target cancer cells as compared wit a control non-cancer cell; determining the protein corresponding to said identified polynucleotide; determining if said protein is

immunogenic comprising the steps of introducing a gene transfer vector containing a polynucleotide encoding said protein into a antigen presenting cell under conditions whereby said polynucleotide is expressed by said antigen presenting cell; culturing naive immune effector cells with said antigen presenting cells under conditions whereby said naive immune effector cells are educated to recognize antigens presented on the surface of said antigen presenting cell in the context of an MHC molecule; determining if said educated immune effector cells can lyse said target cancer cells, whereby the ability of said protein to elicit an immune response against said target cancer cell is indicative of a putative cancer therapeutic.

Scanlan et al disclose a method for identifying therapeutics applicable to a greater number of cancer patients (column 2, lines 17-27) comprising screening for cancer associated antigen genes in samples taken from patients (column 13, line 61 to column 14, line 8). Scanlan et al disclose a specific example wherein the controls were taken from normal tissues (column 36, lines 25-29). Scanlan et al disclose that the cancer associated antigens were tested for immunogenicity by the serex method (column 37, lines 34-40, thus fulfilling the specific embodiment of first identifying cancer associated antigens which are uniquely expressed or overexpressed relative to non-cancerous cells and secondly determining the immunogenicity of the antigens isolated by the first screen. Scanlan et al disclose that a polypore vaccine may be constructed by linking together of numerous cancer associated antigens isolated by the disclosed methods (column 16, lines 30-46) thus fulfilling the specific embodiment of claim 7 specifying the designing of a cancer vaccine. Scanlan et al disclose the administration of CTL which recognize the cancer associated antigen-MHC complex, thus fulfilling the specific embodiment of claim 4 specifying the administration of effector cells. Scanlan et al disclose the transfection of antigen presenting cells such as dendritic cells to activate a CTL in vitro (column 27, line 3 to line 22), thus fulfilling the specific embodiment of claims 25 and 26 specifying the introduction of a gene transfer vector into an antigen presenting cell and a dendritic cell, respectively.

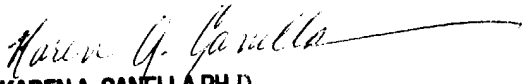
11. All other rejections and objections as set forth in the previous Office action are withdrawn.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/12/2004



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PRIMARY EXAMINER